Medical and Pediatric Oncology 29:228–235 (1997)

PROCEEDINGS OF THE TUMOR BOARD OF THE CHILDREN'S HOSPITAL OF PHILADELPHIA

Giulio J. D'Angio, MD,* Series Editor, and Audrey E. Evans, MD, Associate Editor

Mediastinal Endodermal Sinus Tumor

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Key words: yolk sac tumor; Teilum tumor; non-gonadal germ cell tumor

Lisa Michaels, MD (Fellow Pediatric Oncology/ Hematology)

The patient is a 16-year-old, previously healthy, Hispanic male who presented to his local physician with a 1 month history of weight loss, fatigue, and dyspnea on exertion. Initial evaluation revealed a hemoglobin of 5 g/dl, red cell microcytosis, and low serum iron. An upper GI barium study demonstrated compression of the mid and distal esophagus. The patient then was "lost to follow-up."

One month later, the patient began to suffer worsening cough and dyspnea. He was seen in a local emergency room with complaint of shortness of breath, and pressure in his chest.

Physical examination revealed a pale, agitated young man. The patient was tachypneic with a respiratory rate of 40/min. The heart rate was elevated at 130/min. Blood pressure was 120/80 mm/Hg. Breath sounds were decreased on the left, and heart sounds were distant and muffled. There was no lymphadenopathy and the liver and spleen were not enlarged.

Laboratory studies included a complete blood count with hemoglobin 6.7 g/dl, platelets 178,000/mm^3, and white blood cell count 16,400/mm^3 with a differential of 82% neutrophils, 14% lymphocytes, and 4% monocytes. The LDH was elevated at 1,253 UL and the uric acid was normal. Chest roentgenograms demonstrated a large anterior mediastinal mass, right pleural effusion and cardiomegaly. An ECG was notable for decreased voltages in all leads. Echocardiogram revealed a large pericardial effusion (est. 600cc) and compression of the right ventricle by the large mediastinal mass.

During transport to our hospital, the patient required emergency tracheal intubation for increasing agitation and hypoxemia. Additional studies obtained after arrival here included thoracentesis and pericardiocentesis. Both pleural and pericardial samples were grossly bloody without malignant cells. Bone marrow aspirate and biopsy were normal. Imaging studies of the chest again showed a large anterior mediastinal mass which was compressing the distal trachea and both mainstem bronchi resulting in severe obstruction of the airway.

A single dose of methylprednisolone (1 mg/kg IV) was given without discernible improvement in the patient's tenuous clinical state, nor was there laboratory evidence of tumor lysis. The patient continued to deteriorate, requiring increasing ventilatory support and the addition of inotropic agents to improve perfusion of the extremities.

The general surgery, pulmonary, and anesthesiology services were consulted and an open biopsy of the mass was obtained the following day. The mass was identified as a yolk sac (endodermal sinus) tumor.

Alpha-fetoprotein (AFP) was subsequently found to be 3,823 ng/ml; Beta hCG (HCG) was normal.

Dr. Long, could you review the findings in this patient?

Frederick Long, MD (Radiology Fellow)

The plain films showed an anterior mediastinal mass compressing the trachea and carina with opacification of the right lower lung (Fig. 1). Fluid accumulation and atelectasis appeared likely to be responsible for at least part of the findings on the right. A follow-up MRI clarified this situation (Fig. 2). There is no aeration in the right

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Received 29 March 1996; Accepted 6 May 1996

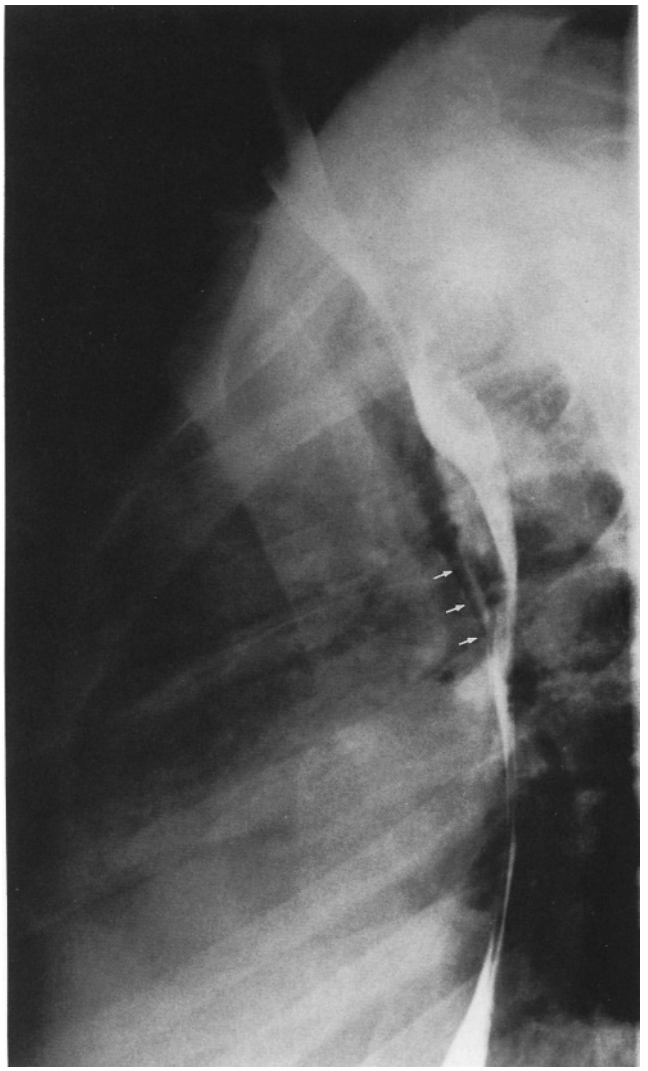

Fig. 1. Lateral chest radiograph with barium in the esophagus. An anterior mediastinal mass is visible, compressing the trachea at the carina posteriorly (arrows).

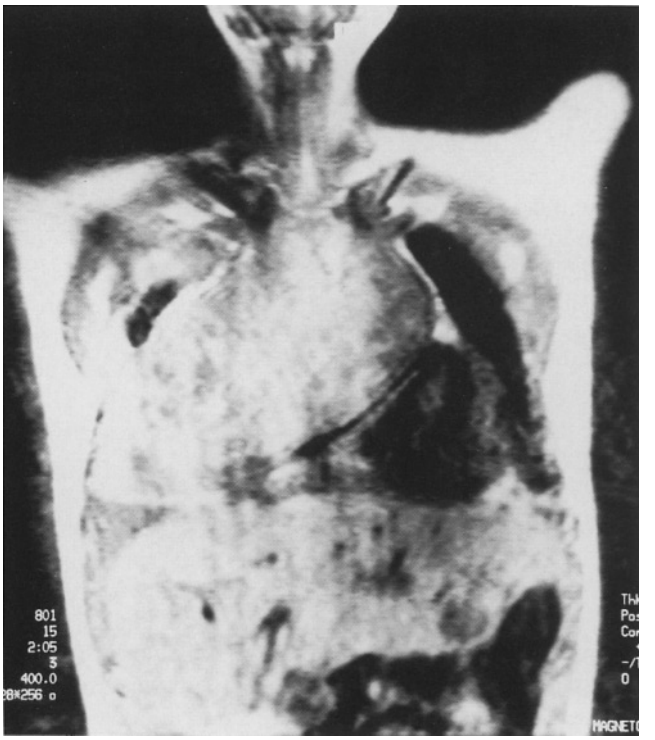

Fig. 2. MRI of the thorax. Motion artifacts are seen. A huge intrathoracic mass is visible extending to the right lateral chest wall and opacifying most of the right hemithorax.

lower lobe secondary to compression by a large mass extending along the right side from the superior anterior mediastinum downward to the diaphragm on the right. Quite surprisingly, the superior vena cava is patent even though encased by the process. The tumor mass abuts the cardiac silhouette, and while there appears to be a line of demarcation, pericardial involvement cannot be ruled out.

Marta Rozans, MD, PhD (Fellow, Pediatric Oncology/Hematology)

What is the differential diagnosis based on the imaging studies?

Dr. Long. Tumors in the anterior mediastinum in adolescent boys most commonly are lymphomas involving the thymus, and that always must be high in the differential diagnosis. However, the extension of this lesion well beyond the region of the thymus casts doubt on that primary diagnosis. Other tumors that present in the anterior mediastinum include thymomas, teratomas, and monophasic germ cell neoplasms such as yolk sac tumors or seminomas. No differentiation is possible on the basis of these imaging studies, of course, but choriocarcinomas most commonly give rise to bloody pleural fluid.

Anna Meadows, MD (Pediatric Oncologist)

Actually, examination of the fluid proved helpful in the differential diagnosis in that there were no cells consistent with a lymphomatous process visible in the pleural fluid. This made the diagnosis of lymphoblastic lymphoma less likely and a tissue diagnosis was needed in order to institute appropriate therapy. Before turning to that, one puzzling feature is the low hemoglobin. Dr. Long, is there any evidence there was a hemorrhage or hematoma anywhere in the chest?

Dr. Long. No, there isn't. The mass has a quite heterogeneous appearance, and although there may be areas of hemorrhage in the mass, there is no suggestion of a large accumulation of blood.

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

This patient exemplifies one of the major therapeutic dilemmas in pediatric oncology. There is a wish to obtain a definitive diagnosis on the one hand. On the other, the hazards of giving anesthesia to patients with the superior mediastinal syndrome are well known [1]. Often treatment must be initiated without a definitive diagnosis. Techniques for using radiation therapy in manners that do not preclude adequate tissue for biopsy have been described. Giving steroids to off-set any edema caused by the disease, or that might be precipitated by radiation therapy is to be avoided, of course. Lymphomas can "melt away" in a few hours, leaving only ghost cells. Given these problems in management, would you please review the decisions made and the steps taken in this particular patient for us, Dr. Rozans?

Dr. Rozans. First, radiation therapy does appear to have a role in enigmatic cases. Here, as Dr. Meadows has pointed out, the diagnosis of lymphoblastic lymphoma was less likely because of the negative pleural fluid. There therefore was no clear contraindication to the use of steroids or other chemotherapeutic agents, so carboplatin and etoposide were administered. Next, a decision had to be reached between percutaneous (needle) biopsy or open biopsy. A needle aspirate might be enough, for example, to establish the presence of a lymphoma, but this was not felt to be a lymphomatous process.

Dr. D'Angio. There is also the risk of inducing a pneumothorax by inserting a needle and is something best avoided in a patient with respiratory compromise, especially since there is no guarantee that the sample would be adequate for diagnosis. The anesthesia department is very well aware of the hazards entailed in anesthetizing patients such as this. However, even with all measures taken to guard against respiratory compromise, one boy in our experience died on the operating table. He had a classic anterior superior mediastinal mass compressing the trachea. What wasn't appreciated preoperatively was the cardiac and pericardial infiltrate that rendered the cardiac structures rigid. He succumbed because of peripheral vasodilation secondary to muscle relaxants and the anesthesia itself, and died of "forward failure," despite the frantic efforts of the operating team to maintain adequate ventilation. Unfortunately that wasn't the problem.

It is certainly worth emphasizing that it is not a casual decision to proceed with open biopsy under anesthesia in a patient such as this. The risks and benefits need to be weighed extremely carefully.

Dr. Rozans. It is time to review the results of that biopsy.

Jane Chatten, MD (Pediatric Pathologist)

The specimen was about 3 ml in total volume, and consisted of tan and slightly mucoid fragments, with no suggestion of cyst formation or a mixture of elements. Frozen section showed a malignant epithelial tumor and samples were set aside for the tissue bank. The remainder was used for histology, and showed the microcystic and trabecular pattern of pale frothy cells characteristic of endodermal sinus tumor (Fig. 3). Cytoplasmic inclusions of alpha-fetoprotein (AFP) were not conspicuous, but immunohistochemical stains were not considered necessary.

Whether this tumor type was monomorphous or a component of a teratoma or mixed germ cell tumor—seminomatous, embryonal, and choriocarcinomatous elements all being rare but possible—obviously cannot be decided by a relatively small incisional biopsy. The homogeneity of imaging studies suggests there is no mature, cystic teratoma present, and the presence of other malignant germ cell components would not change therapy anyway, as far as I know.

Garrett Brodeur, MD, PhD (Pediatric Oncologist)

Regarding the role of radiation therapy: chemotherapy alone might prove adequate under these circumstances.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

That is certinaly true. Unfortunately, one can never know in the individual case. In a patient like this one, who was desperately ill, it seemed best to proceed with combined modality to ensure the most rapid response possible. The strategy is to give that amount of radiation therapy which, combined with chemotherapy, will at least stabilize the situation if not reverse the ominous clinical picture. Accordingly, 200 cGy were given on each of 4 days, each additional dose being monitored carefully according to the clinical and laboratory signs of improvement. Radiation therapy was suspended after the delivery of 800 cGy because the child's condition seemed to be improving.

Dr. Michaels. There has been gradual improvement. The legs are now being perfused adequately, for example.

Dr. Meadows. We might consider the choice of chemotherapy regimens. Are there any drugs other than those employed that hold promise?

Nancy Bunin, MD (Pediatric Oncologist)

Not really. There is a POG/CCG study that includes etoposide, cisplatin, and bleomycin. The cisplatin regimen is randomized between standard and intensive dosing. Especially in Europe, carboplatin has been substituted for cisplatin, and, in preliminary analyses, appears to yield equally good results. Bleomycin had perhaps best be withheld in this patient until radiation therapy is no longer a factor, and pulmonary compromise improves.

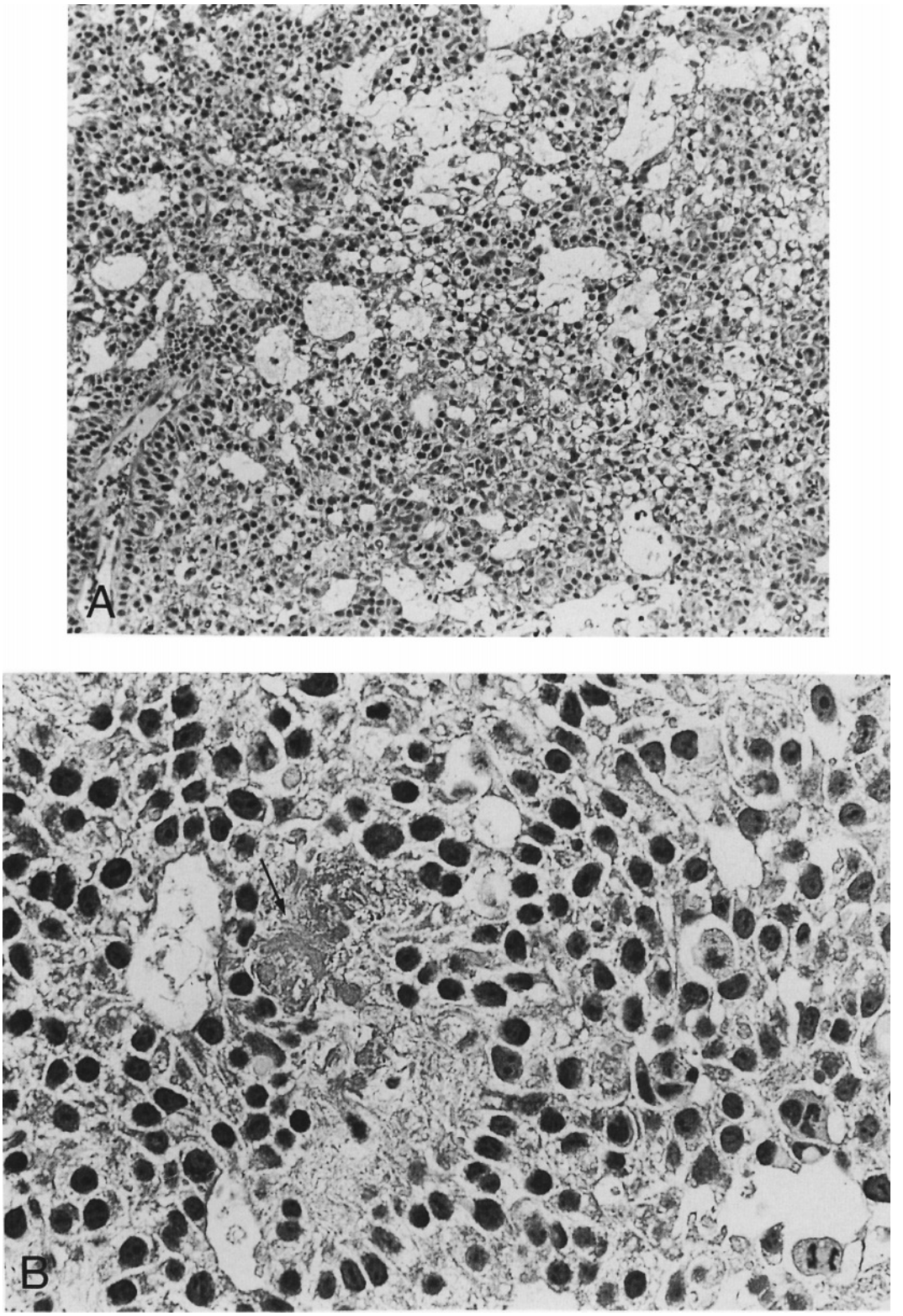

Fig. 3. **A:** Low power view shows a generalized vesicular pattern and uniform, pale to vacuolated cells with some perivascular accentuation (lower left). Original magnification, ×50. **B:** Higher magnification shows nuclei with prominent nucleoli, pale cytoplasm, and aggregate of apparent basement membrane material (arrow). Original magnification, ×200.

Richard Womer, MD (Pediatric Oncologist)

It should be mentioned that the AFP level is an important criterion of tumor response—indeed, of prognosis. It has been shown that a prolonged and slow drop in the AFP level is associated with a worse prognosis than a prompt reduction according to the known half-life of the marker.

Dr. Brodeur. Another prognostic factor is the site. There is a much better outlook for patients who have gonadal endodermal sinus tumors vs. those that arise in non-gonadal sites—perhaps 90% survival vs. 50–60%, respectively.

Dr. Bunin. Maybe the difference will no longer be so marked now that more effective chemotherapy regimens employing cisplatin and etoposide are available.

Dr. D'Angio. What are your plans for this patient, Dr. Rozans?

Dr. Rozans. First, it might be useful to review what is known about endodermal sinus tumors in general, and those that arise in the mediastinum in particular. There are not many reports that are helpful under these particular sets of circumstances, however.

Germ cell tumors account for approximately 3% of pediatric malignancies, with an annual incidence of $4.2/10^6$ children under age 15 years. Germ cells are totipotent cells that can first be identified in the fetus at about 4 weeks of age, located in the yolk sac. By 6–8 weeks, they have migrated to the urogenital ridge, where they will develop into the rete testis and seminiferous tubules (male) or into the ovarian follicles (female). At the time of migration, the gonadal ridge extends from about C6 to S2, and failure of complete migration of these germ cells may result in extra-gonadal germ cells anywhere in this area. Germ cell tumors may be gonadal (testicular or ovarian) or extra-gonadal, or they may develop from fetal trophoblastic tissue. They may be benign or may undergo malignant transformation; in addition, they can be of mixed types.

There are six histologic subtypes of germ cell tumors in children:

I. *Teratoma*—Classically defined as being composed of all three embryonic germ layers (endoderm, mesoderm, and ectoderm), but may more broadly be considered to have developed from pluripotent cells and contain several tissue types foreign to the type in which it has arisen. There are subsets:
   A. Mature—benign tumor with well differentiated tissue types;
   B. Immature—borderline lesions. Some certainly undergo malignant transformation;
   C. Malignant—clearly malignant germ cell components are present.

II. *Germinoma*—These are derived from primordial germ cells prior to embryonal differentation. They have been called seminoma when they arise in the testes, and dysgerminoma when ovarian in origin. They are typically found in the mediastinum, pineal, and supra-sellar regions as well as gonad, especially in the undescended testicle.

III. *Embryonal carcinoma*—It is often poorly differentiated and may exhibit extensive necrosis. It does not produce AFP and is usually HCG negative.

IV. *Endodermal sinus tumor* (EST)—Also called yolk sac tumor or yolk sac carcinoma. Unlike embryonal carcinoma, EST has extraembryonic differentiation. It is the most frequent malignant germ cell tumor in children, with the most common sites being sacrococcygeal (infants) and ovary (adolescents), but may also occur in the testis. The mediastinum is a relatively uncommon location, as are intracranial, retroperitoneal, and vaginal primary sites.

V. *Choriocarcinoma*—A neoplasm that also has extraembryonic differentiation. It occurs in two distinct forms: gestational and nongestational. It is an uncommon tumor, and the two forms have very different behaviors and responses to therapy.

VI. *Gonadoblastoma*—It occurs almost exclusively in dysgenic gonads (i.e., 46XY gonadal dysgenesis, and 46XY/45XO mosaic) and generally does not spread distantly.

Germ cell tumors may produce several proteins that have been useful tumor markers for diagnosis and clinical evaluation of therapy. Alpha-fetoprotein is the fetal equivalent of albumin, and is present in the serum in high amounts during fetal life, falling to adult levels by 7–10 months of age. AFP is also expressed by hepatocellular carcinoma, hepatoblastoma, other GI malignancies, and several non-malignant states. Its half-life is 4 to 7 days in the adult, but varies during the first 4 months of life. It is expressed by endodermal sinus tumors, and generally not by other germ cell tumors. Beta-HCG is normally made by the placenta, and is therefore a feature of choriocarcinoma (which has extra-embryonic differentiation).

After Teilum's seminal paper [2], mediastinal endodermal sinus tumor was first described in 1967 by Teilmann et al. [3] in a 33-year-old man who died shortly after presentation. It continues to be an uncommon diagnosis found nearly always in males.

In 1986, Truong et al. [4] reported seven patients with mediastinal endodermal sinus tumor, and reviewed the literature. At that time, only 49 patients with mediastinal EST had been reported, most having symptoms of a mediastinal mass for less than 3 months. Elevated AFP (380 ng/ml to 50,000 ng/ml) was present in more than 85% of the patients, whereas HCG was elevated in only 10%. Our young man, therefore, had a typical presentation of an unusual disease.

There have been a few case reports of patients with mediastinal EST presenting with problems similar to those of the patient presented today. A 1985 report from Chicago [5] tells of a 16-year-old male with a history of resection of a mediastinal mass, who re-presented with respiratory distress, the superior vena cava (SVC) syndrome and a large mediastinal mass. Since pathology from the initial tumor was consistent with EST and the patient had an elevated AFP, biopsy was not undertaken. He was treated with radiation therapy to 4,225 cGy to the mediastinum and with chemotherapy, consisting of cyclophosphamide, vinblastine, dactinomycin, bleomycin, and cisplatin. His SVC syndrome resolved in a few days, and he had near complete disappearance of the tumor without surgery. Metastases were noted a few weeks later, and he died of disease 8 months after presentation. The testes were normal at autopsy.

Willoughby [6] reported another case in 1987. This was a 10-year-old girl (!) who presented with 2 days of dyspnea and 1 month of weight loss. On examination, the child was dyspneic in all positions and cyanotic. Chest roentgenogram and CT scan showed a mediastinal mass compressing the trachea just above the carina, and multiple pulmonary nodules. Pelvic imaging showed an enlarged ovary. A percutaneous needle biopsy was done with minimal sedation, followed immediately by mediastinal irradiation of 300 cGy/day $\times$ 4 days. A "good" clinical response was noticed by day 3, and chemotherapy with cisplatin, vinblastine, and bleomycin was started on day 6 (the pathology was EST). After three cycles of this chemotherapy, alternating vincristine/dactinomycin/cyclophosphamide, and vincristine/doxorubicin/dactinomycin courses were given for a total of 18 months of chemotherapy. She had no evidence of disease at the time of the report, 12 months after completing chemotherapy. Complications included SIADH and seizures, an ocular metastasis treated with radiation, and prolonged marrow aplasia. AFP fell from about 300,000 ng/ml at presentation, to normal levels according to its half life.

These two reports suggest that radiation can indeed be helpful in the emergency management of mediastinal endodermal sinus tumors.

Since these intrathoracic neoplasms are so rare, it is difficult to find studies that include enough patients from which to draw firm conclusions. For example, Logothetis et al. reported 49 patients with extra gonadal germ cell tumors, only five of which were mediastinal ESTs [7].

A helpful report is from the University of Indiana, where Saxman et al. reviewed their experience with 21 patients with mediastinal EST treated between 1976 and 1988 [8]. At the time of that publication, there were only 66 reports of primary mediastinal EST in the English literature. Fourteen of the patients were newly diagnosed, and seven were referred because of relapse. All patients were male, and only patients with pure ESTs were included. Of the 14 patients with new diagnoses, three had thoracotomy and complete excision, and 11 had biopsy only. They were all treated with four cycles of cisplatin, bleomycin, and vinblastine or etoposide. Some patients then underwent thoracotomy and resection of residual masses, followed by additional chemotherapy with or without radiation therapy. Seven patients died of disease, five were long-term survivors without disease (33–140 months), one was alive with disease, and one died of possible bleomycin toxicity. Of note, one of the survivors had had a relapse that was successfully treated with bleomycin, etoposide, cisplatin, and radiation. All seven patients referred because of relapse were treated with cisplatin with or without other drugs, and all died.

Recently, an association between mediastinal endodermal sinus tumors and acute myelogenous leukemia (AML) has been noted. Nichols et al. reported several patients with both malignant mediastinal germ cell tumors and hematologic malignancy [9]. Between 1976 and 1988, 31 patients with primary mediastinal germ cell tumor were evaluated and treated. All received cisplatin-based chemotherapy, and five (5/31 = 17%) subsequently went on to develop a hematologic malignancy. Eleven additional patients with both diseases were subsequently referred to the authors.

The median time to onset of the hematologic problem was 6 months (range 0–122 months); five had simultaneous onset of both diseases. Of the total, six patients had M7 (megakaryoblastic) AML, two each had myelodysplastic syndrome with abnormal megakaryocytes, megakaryocytic myelosis, and essential thrombocythemia. One patient each had M4 (myelo-monoblastic) AML, M5 (monoblastic) AML, mixed lineage leukemia, and undifferentiated leukemia. Cytogenetic analysis was done in 10 patients: three had trisomy 8, one had Kleinfelter's syndrome, and one had isochromosome 12p, which has been clearly associated with germ cell tumors. The authors note (1) the very short latent period between the diagnosis of germ cell tumor and the hematologic malignancy (often simultaneous, in fact); (2) the isochromosome 12p found by them and others in the leukemic cells; and (3) the types of leukemia found, which are unusual for secondary cancers. They suggest, therefore, that the malignant hematopoietic diseases seen actually develop from the germ cell tumor, and are not caused by chemotherapy.

Orazi et al., also from Indiana, tested the above hypothesis by examining mediastinal germ cell tumors from six patients who later developed leukemia [10]. They found morphologically identifiable hematopoietic cells within four of the six tumors; three were poorly differentiated blasts, and one was composed of clusters of erythroid precursors. Bone marrow and tumor hematopoietic cells were morphologically similar, and the hematopoietic nature of the cells was confirmed with immunohistochemis-

try, with or without flow cytometry. Two of the patients had isochromosome 12p in both the germ cell tumor and the leukemia. These data suggest that mediastinal germ cell tumors can differentiate along hematopoietic lines. It is not clear if the leukemia developed after initiation of normal differentiation, or if malignant transformation occurred first followed by limited differentiation.

Getting back to the management of our patient, we opted to treat him with carboplatin and etoposide, with plans to add bleomycin after his pulmonary status stabilizes some more, as Dr. Bunin suggested earlier.

Dr. Bunin. There remains a question of whether surgery should be used and whether additional radiation therapy is indicated. Personally, I would advocate early removal of the tumor.

Dr. Goldwein. One of our objectives in radiation oncology is to treat the smallest possible volume consistent with inclusion of known disease. Whether the child should receive additional radiation therapy will depend on the tumor response to chemotherapy, whether there is any residual disease after surgery—if and when it takes place—and the like.

Dr. Brodeur. Let me return for a moment to initial management. AFP levels are available in a few days. Once lymphoma was ruled out, might the serum markers HCG and AFP not be adequate for making a specific diagnosis? As Dr. Rozans pointed out, HCG levels identify choriocarcinoma, while a positive AFP establishes the diagnosis of endodermal sinus tumor (or possibly embryonal carcinomas), granted there is no evidence of a liver primary.

Dr. Meadows. That is right. These relatively simple and available laboratory tests might well make it possible, in future patients, to avoid open thoracotomy with all the hazards that have been discussed.

ADDENDUM

After initial improvement, the patient's clinical condition deteriorated and could not be reversed. Imaging studies showed continuing enlargement of the tumor. Life support measures were discontinued and the patient died 14 days after admission. Consent for postmortem examination was not obtained.

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SERIES EDITOR'S NOTE

There are several abbreviations and signs that are often used in manuscripts. Among the most common is *et al.*, but the punctuation is frequently misused. The Latin *et*, of course, is "and," and requires no period. On the other hand, *al.* is an abbreviation of the Latin *alii* (others) and requires a period. *Et al.* therefore literally stands for "and others." Other useful abbreviations are *v.s.* for *vide supra* or "see above," *v.i.* for *vide infra*, or "see below," *e.g.* (*exempli gratia*) meaning "for example," and *i.e.* (*id est*) for "that is." *Viz.* is a little different from *i.e.* in meaning. It stands for *vide licet*, and comes from *videre licet* or "it is permitted to see." It has the sense of "namely," or "by which is meant."

The "&" sign is termed the "ampersand," an abbrevation of "and per se and," which is a little opaque but means, "and the sign, used by itself, stands for and." It can be coupled as *&c.* to mean, *et cetera* (*etc.)* (and so forth). The "/", commonly called a "slash" or "stroke" technically is the *virgule* (Latin: little rod). In English, it is used for many purposes: to indicate a fraction (x/y), to separate two or more component parts (psychologic/social/economic factors), or in either-or constructs such as "and/or." In at last one language (Hungarian), the virgule seems to be used instead of quotation marks; which in Italian, are called *virgolette* (teeny rods), while *virgola*, obviously from the same stem, means *comma* (Greek *komma* = short clause) and is used to separate elements of a single thought. The colon (:) from the Greek *kolon* implies that a list or explanatory comment follows, whereas the semicolon (;) is used to separate distinct but

related statements in the same sentence. Very often, a period (Greek *periodos*) and a new sentence would do as well.

A dash (—) can also be used to separate two thoughts; or indeed, can be employed to separate a parenthetical remark from the main content of a sentence. Curved lines: ( ) (parentheses or brackets), are more often employed to enclose a *parenthesis* (Greek: to insert beside), but square brackets or braces—[ ]—can be used instead or when the parenthesis contains an even more subordinate thought. Then, in one convention, brackets are used to enclose the entire parenthesis, and the curved lines, the insert within the insert. Finally, the *hyphen* (-) connects the parts of a compound word. For example, in speaking of a dog's dental array, one would describe a hound's tooth, but there is a pattern called a hound's-tooth check, too; or, one can *do good,* and thus become a *do-good* person, perhaps by baking an *apple pie* for a gift and leaving the kitchen in *apple-pie* order. The rules for hyphenating words, never entirely clear, are understandably less and less observed, however, and the two elements are now often left unhyphenated or at times are fused into a single word. One dictionary at hand uses "back-formation" to describe a derived word, while another leaves the two words separate.

Finally, although not so much seen in manuscripts, the ℞ sign is seen daily by most physicians. The origin of ℞ in writing prescriptions is obscure. It has the meaning of "take" from the Latin *recipe.* The sign itself is thought by some to derive from the similar symbol for Jupiter, the supreme Roman deity. Therefore, according to this explanation, writing ℞ propitiates (appeases) the god when a prescription (from Latin: to *write before* having the sense of "to order") is written.

It is both proper and prudent (because potentially prophylactic) to use abbreviations and punctuation marks correctly. Appropriate usage might prove propitiatory for editors and copy readers—and probably reviewers, too.